II. Remarks

No new matter is added by the above amendments and new claims.

A. The Office Action Fails to Articulate the *Graham* Factors

As an initial matter, Applicants respectfully note that the rejections under 35 USC §103 are deficient for (i) failure to articulate the scope and contents of the prior art and (ii) failure to determine the "level of ordinary skill in the art", both of which are required under *Graham v. John Deere*, 383 U.S. 1 (1966). *See* MPEP § 2141.

As discussed in the Expert Declaration of Dr. Robert Lochhead, submitted pursuant to 37 CFR § 1.131, the Prencipe reference relates to a specific type of oral care composition – a whitening (*i.e.*, bleaching) toothpaste – and would not be pertinent to a person having ordinary skill in the art – here, a formulator of cosmetic or dermatological products to be applied to the hair, skin or nails – who was seeking a solution to the problems of reducing irritancy, increasing shelf life and providing precise dosing of two otherwise incompatible topical active ingredients.

For the following additional reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been made. Under 35 USC § 103, a *prima facie* case obviousness is established when three criteria are satisfied. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to a person of ordinary skill in the art, to modify the teaching of an individual reference or to combine the teachings of more than one reference. Third, there must be a reasonable expectation of success. *See* MPEP § 706.02(j).

B. All Claim Limitations Are Not Taught or Suggested by Prior Art References

In order to find obviousness, each claim element must be taught or suggested in the prior art references. As discussed below and in the Declaration of Dr. Lochhead, several required essential claim elements are neither taught nor suggested by the cited prior art.

i. "water-based carrier bases having substantially the same lipophilicity"

With respect to Claim 1 (and its dependent claims), none of the cited references teach or suggest the required element that both of the active ingredient-containing formulations for topical administration to a patient comprise water-based carrier bases having substantially the same lipophilicity. The Office Action expressly notes the absence of this required claim element from two of the primary references that form the basis for the rejection – US Patent No. 6,106,812 ("Prencipe") and WO 9315726 ("WO26"). Instead, in Paragraph 3 on Page 3, the Office Action makes a conclusion not otherwise supported by the record – namely, that "the two compositions of the two components (table 1) ... do not appear to vary in their hydrophilicity or lipophicility."

Applicants note that it unclear what is meant by "table 1", since both Prencipe and WO26 contain a "table 1". However, only table 1 of Prencipe contains multiple formulations on which a comparison could be made vis-à-vis lipophilicity. Further, Page 3 of the Office Action discusses the component ingredients of both compositions of Table 1 with respect to Prencipe and not WO26. Therefore, for purposes of this Response, Applicants assume that the above-quoted statement is with respect to Table 1 at Column 7 of Prencipe.

As discussed at Paragraph 14 in the Lochhead Declaration, lipophilicity depends on partition coefficient which, in turn, depends upon solubility. At Paragraph 18 of his Declaration, Dr. Lochhead analyzes the gel and paste compositions taught in Table 1 of

Prencipe and concludes that they vary considerably in their constituent ingredients and, therefore, in their lipophilicity.

For example, Paste A-1 is comprised of 12% glycerin and 22.6% sorbitol. In contrast, Paste A-2 is comprised of 20% glycerin and 9% sorbitol. The gels taught in Table 1 contain glycerin at levels from 30% to 40% by weight of the composition. The glycerin concentrations in the gels are thus significantly higher – from 50% to over 333% – than the pastes. These differing glycerin levels would, according to Dr. Lochhead, result in different partitioning of the active ingredients. In this regard, Applicants also refer to Paragraph 16 of the Lochhead Declaration, which shows that benzoyl peroxide is almost 100,000 percent more soluble in glycerin than it is in water.

The gels in Table 1 of Prencipe do not contain sorbitol, but instead contain polyethylene glycol (PEG). According to the American Pharmaceutical Association *Handbook of Pharmaceutical Excipients*, p. 597 (4th Ed. 2003), at 20°C the solubility of sorbitol in water is 1 in 0.5. These solubility differences would result in carriers having different partitioning of the active ingredients contained therein. In Paragraph 19 of his Declaration, Dr. Lochhead states that replacement of sorbitol by polyethylene glycol will result in different partitioning of ingredients and, as a consequence, different lipophilicities of the aqueous carrier bases.

Paragraph 16 of Dr. Lochhead's Declaration shows that benzoyl peroxide is 25 million percent more soluble in PEG 400 than in water. As Dr. Lochhead explains, the mere addition of 10 percent PEG-400 to water raises the solubility of benzoyl peroxide by 241 percent. As further explained by Dr. Lochhead, the solubility of benzoyl peroxide in propylene glycol is almost two million percent more than it is in water.

For the following additional reason, the formulations taught in Table 1 of Prencipe would not have substantially the same lipophilicity as claimed in the present application.

The water content of the two types of compositions (gel and paste) taught in Prencipe differ considerably. Prencipe's Table 1 teaches the combination of Paste A-1 with Gel B. Paste A-1 contains 12% glycerin, 22.6% sorbitol, and 10.3% water. Gel B contains 40% glycerin, 10% polyethylene glycol (PEG), and 39.9% water. As explained by Dr. Lochhead in Paragraph 18 of his declaration, these two compositions would not have "same lipophilicity" as it is defined by the specification of the pending application.

ii. "polymeric delivery system"

Another required claim element – one not disclosed in either of the two primary references (Prencipe or WO26) – is that at least one formulation contains a polymeric delivery system. As explained in Paragraphs 7 – 11 of the Lochhead Declaration, a person of ordinary skill in the art would understand that not all "polymers" are "polymeric delivery systems". This understanding would be reinforced by Paragraph [0050] of the pending application, which describes a "polymeric delivery system" as one capable of delayed release of an active ingredient.

As further explained by Dr. Lochhead in Paragraph 10 of his declaration, three of the gel compositions in Table 1 of Prencipe (Gels B, D and E) contain a synthetic polymeric thickening agent, Carbopol 974P, and two of the pastes in Table 1 of Prencipe contain a natural polymeric thickener, carboxymethylcellulose ("CMC"). (Carbopol is the commercial name for a family of carboxyvinyl polymers. *See*, Prencipe, Col. 3, lines 34 – 36.) However, as Dr. Lochhead explains, neither Carbopol nor CMC is a polymeric delivery system.

The Office Action also notes that the examples taught at pages 11 – 12 of WO26 contain an active ingredient (benzoyl peroxide), water and a polymer. Examples 1 – 4 on Page 11 do not contain any polymers. Examples 5 – 9 on Page 12 contain

carboxyvinyl polymers which, as discussed in the preceding paragraph and in Paragraph 11 of the Lochhead Declaration, are not polymeric delivery systems.

iii. "substantially the same water content"

Claim 23 of the pending application recites a product where the first and second formulations have substantially the same water content. As shown in the following table, and discussed in Paragraph 26 of the Lochhead Declaration, the water content of the two compositions taught in Table 1 of Prencipe are not substantially the same:

	Paste A-1	Paste A-2	Gel B	Gel C	Gel D	Gel E
Water Content	89.3	89.7	60.2	69.1	57.8	49.9

iv. "substantially the same viscosity"

Claim 24 of the pending application is directed to a product where the first and second formulations have substantially the same viscosity. The two pastes in Table 1 of Prencipe contain binding/thickening agents – "Gantrez liquid" and carboxymethylcellulose. These ingredients are not, however, present in the gels. As explained by Dr. Lochhead in his declaration, the viscosity of the two compositions taught in Prencipe (i.e., paste and gel) would not be substantially the same and, indeed, would differ significantly. See Paragraph 27 of Lochhead Declaration.

The WO26 reference is directed to two compositions – the first, an aqueous solution of clindamycin; the second, an aqueous suspension of benzoyl peroxide. These two compositions are further taught to be combined into a final topical composition. WO26 teaches that the viscosity of the benzoyl peroxide component is usually from 50,000 – 90,000 cps, more preferably from 65,000 to 85,000 cps, and that the final topical composition has a viscosity of 70,000 to 120,000 cps, preferably from 80,000 to 100,000 cps.

While the WO26 does not teach the viscosity of the clindamycin-containing solutions (WO26 Examples 1 – 4), the solutions do not contain any thickener, but do contain 85 to 97 percent water. As explained by Dr. Lochhead at Paragraph 27 of his declaration, these clindamycin solutions would possess a substantially lower viscosity than the benzoyl peroxide suspensions of WO26 Examples 5 – 9. Dr. Lochhead estimates that the clindamycin solutions of Examples 1 – 4 would have viscosities of less than 100 cps. Accordingly, WO26 does not teach or suggest to combining two component compositions with substantially the same viscosity into a single final product.

C. No Motivation to Combine; No Reasonable Expectation of Success

The teaching or suggestion to (i) modify a prior art reference or to combine prior art several references and (ii) the reasonable expectation of success from doing so must both be found in the prior art and not based on an applicant's disclosure. *See* MPEP § 2144.08, Part II A (citing *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that [the modification/combination] should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.")) *See also*, MPEP § 706.02(j) (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.))

The Office Action rejects claims 4, 8-22 and 24-28 of the patent application under 35 USC §103(a) as being unpatentable over WO26 in view of two secondary references, Wester and European Patent Application EP306236 ("hereinbelow EP236"). At Page 4, the Office Action concludes that it would have been obvious to the person having ordinary skill in the art at the time of the invention to employ a microsponge polymeric

delivery system (as disclosed in the article by Wester *et al.* and EP236) in "the composition of WO26".

As noted above, however, WO26 does not teach or suggest (i) the use of polymeric delivery systems *per se* or (ii) combining two compositions having substantially the same lipophilicity. *See also*, Lochhead Declaration at Paragraph 30. Moreover, the Office Action is silent on whether, and on what basis, there would be reasonable expectation of achieving topical formulations of the type claimed. The mere possibility that the prior art can be modified does not make the modification obvious unless the prior art teaches or suggests the desirability of the modification. *See* MPEP § 2144.08, Part II A (citing *In re Brouwer*, 77 F.3d 422, 425 (Fed. Cir. 1996)).

As a preliminary matter, Applicants note that the Office Action does not specify what is meant by "the composition of WO26." Applicants respectfully submit that "the composition of WO26" patent could be interpreted in any number of ways by the person having ordinary skill in the art based on the broad guidance offered by the Specification of WO26 with respect to the carrier system. For example, at Page 6, lines 11 – 29, the WO26 reference teaches that the active ingredients will be combined in "a suitable vehicle or carrier, typically an aqueous carrier, and will preferably be further combined with an aqueous gelling agent such as neutral, anionic and cationic polymers, and mixtures thereof ..." While the WO26 identifies two preferred classes of polymeric aqueous gelling agents (Carbopol and cellulosic polymers), it provides minimal guidance on the amount of gelling agent relative to other ingredients. For example, Table 1 of WO26 teaches that the gelling agent may, preferably, be combined in a suspension or solution with 5% – 15% humectant and 0 – 20% solvent. As discussed at Paragraph 31 of the declaration of Dr. Lochhead, choice of solvent, humectant and other auxiliary

ingredients will markedly affect both the aesthetics and performance of topical compositions.

Notwithstanding the observations made in the preceding paragraphs, Applicants note that WO26 contains nine examples – four aqueous solutions of clindamycin phosphate ester (Examples 1 – 4), four aqueous suspensions of hydrous benzoyl peroxide (Examples 5 – 8) and one example of premicronized hydrous benzoyl peroxide (Example 9).

As explained by Dr. Lochhead in his Section § 1.131 Declaration, the rate at which active ingredients are released from a polymer delivery system, such as the microsponge, is based in considerable part, on the carrier system. For example, if the active ingredient in the microsponge is highly soluble in the carrier, the microsponge will "dump" the active earlier than is desired. Similarly, if the solubility of the carrier is lower than desired, delivery can be retarded, diminishing the efficacy of the product. *See* Lochhead Declaration at Paragraph 14.

It is for the above reasons that the two component compositions (at least one containing a polymeric delivery system) according to the present invention are claimed to be in carriers <u>having substantially the same lipophilicity</u>.

As discussed in Paragraph 14 of the Lochhead Declaration, there could be negative consequences (in terms of product efficacy and perhaps safety) if the carriers had differing lipophilicity. Dr. Lochhead describes a two-component product – Composition I (containing an active ingredient entrapped in a microsponge) and Composition II. Where the active ingredient in the microsponge has <u>greater</u> solubility in the carrier of Composition II, mixing of Compositions I and II could result in dumping of the active. In the case of certain actives, this could result in too high a dose and possible adverse health effect. In contrast, where the active ingredient in the

microsponge has lesser solubility in the carrier of Composition II, the rate of delivery of the active from the microsponge could be impeded when Compositions I and II are mixed, resulting in a less efficacious product.

Wester describes a controlled release of benzoyl peroxide in Microsponge formulations but does not disclose a second formulation to be mixed with the benzoyl peroxide formulation. Wester also does not provide a detailed chemical composition for the carriers in these formulations. As discussed in the Declaration of Dr. Lochhead at Paragraph 31, the nature, type and concentrations of excipients in the carrier base would be highly pertinent to a person having ordinary skill in the art. Since excipients (thickeners, solvents, humectants or other auxiliary ingredients) would affect the aesthetic attributes and performance of a topical composition, a sufficiently detailed disclosure with respect to the excipients would be needed for a person having ordinary skill in the art to have a reasonable expectation of successfully formulating a product of the type claimed in the instant application.

In addition, Wester does not teach or suggest controlling lipophilicity or matching lipophilicity. Nor, in the absence of a second formulation (*i.e.*, to be combined with a first formulation in a final product), would a person having ordinary skill in the art have a motivation based on the teachings of Wester and WO26 to match lipophilicity of two compositions as is taught and claimed in the present application. *See* Lochhead Declaration at Paragraph 32.

Like WO26, EP236 teaches a single formulation containing a polymeric delivery system. The disclosure of EP236 with respect to the carrier is limited. Claim 8 teaches a counterirritant compound in a solvent substantially immiscible with water or a solvent at least partially miscible with water. EP236 does not, however, teach or suggest

matching lipophilicity between two formulations. *See* Paragraph 33 of the Declaration of Dr. Lochhead.

For these additional reasons, Applicants respectfully submit that the Office Action fails to make a *prima facie* case of obviousness and request that the rejections be withdrawn.

D. Amended and New Claims Are Novel and Not Obvious

Applicants respectfully submit that the added limitations of the amended claims and the new claims are neither taught nor suggested in the prior art references cited in the Non-Final Office Action to which this Response is directed.

Claim 1 (and its dependent claims) are now directed to "a pharmaceutical and/or cosmetic product comprising first and second active ingredient-containing formulations for topical administration to the skin, hair or nails of a mammal" (emphasis added). In contrast, the Prencipe reference is directed to oral care compositions. In this regard, Applicants specifically note that Prencipe is directed to whitening the teeth, and nowhere mentions application of the claimed composition to the skin, hair or nails. Based on Paragraph 25 of the Declaration of Dr. Lochhead, applicants respectfully submit that a person having ordinary skill in the art, recognizing the differences in rates of absorption between the oral mucosa and the skin, hair or nails, would not be motivated to modify the teachings of Prencipe to make a skin, hair or nail composition of the type now claimed.

New claims 29 and 30 are now directed to pharmaceutical and/or cosmetic products comprising first and second active ingredient-containing formulations for topical administration, where each of the active ingredient-containing formulations has a viscosity of less than about 40,000 cps and less than about 30,000 cps. Support for these amendments are found in Paragraph [0069] of the pending application which

teaches that formulations of the present invention are more preferably in the range 5,000 to 50,000 cps.

Neither WO26 nor Prencipe teach formulations at these viscosities (*i.e.*, less than about 40,000 cps or 30,000 cps). As discussed above, Page 8 of WO26 teaches topical compositions having a viscosity of 70,000 to 120,000 cps, preferably from 80,000 to 100,000 cps. In Example II (Col. 8, lines 10 -20), Prencipe teaches three gels F, G and H having viscosities of 96,000, 101,000 and 16,000 cps, respectively. Prencipe then describes Gel H (viscosity 16,000) as undesirably having "very little structure" while Gels F and G (having viscosities at or about 100,000 cps) exhibit "acceptable standup." *See*, Col. 8, lines 26 – 67. Prencipe thus teaches away from lower viscosity gels of the type recited in new Claims 29 and 30.

Claim 3 as amended is now directed to a polymeric delivery system comprised of a plurality of crosslinked porous polymer particles forming a porous polymeric matrix in which is contained an active ingredient. Support for this claim is found in Paragraph [0050] of the present application.

Conclusion

For the above reasons, it is respectfully submitted that amended claims are in condition for allowance. Favorable action is therefore earnestly solicited. If the Examiner believes that an interview will expedite allowance, please contact undersigned counsel.

Respectfully submitted,

Dated: October 8, 2007

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